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Research Article

Effect of X-Ray Exposure on Oxidative Stress in Liver and Kidney in Rats in Early Life: An Experimental Study

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Abstract

The aim of this study was to investigate the levels of oxidative stress and antioxidants in the liver and kidney tissue of baby rats exposed to whole-body x-ray by creating a newborn rat model. In this study, 60 baby rats obtained from 15 pregnant rats were used. Pregnant rats were randomly divided into five groups. The control group (Group I) was not subjected to X-ray. The 2nd and 3rd groups were subjected to both intrauterine and postnatal X-ray, and the 4th and 5th groups were subjected to only postnatal X-ray. At the end of the 4-week study period, oxidative stress markers were studied in the liver and kidney tissue. In all groups that received X-ray, an increase in the amounts of malondialdehyde (MDA) and advanced oxidation protein products (AOPP), a decrease in the amount of glutathione (GSH) and catalase (CAT) activity were detected in liver tissues ($P<0.05$), and an increase in the activities of MDA, AOPP and CAT, and a decrease in the amount of GSH were detected in kidney tissues ($P<0.05$). These findings indicate that X-ray exposure in early life disrupts the antioxidant defense system by inducing oxidative stress in liver and kidney tissues, highlighting the necessity of minimizing unnecessary radiation exposure in clinical practice.

Keywords: Antioxidant enzymes; New-born; Oxidative stress; X-ray

Introduction

Although ionizing radiation has tremendous diagnostic and therapeutic benefits for humans, it also has serious harmful effects [1]. Ionizing radiation causes serious damage to living systems by transferring high energy directly to macromolecules or by hydrolysing water. As a result of high energy exposure, it causes excessive production of reactive oxygen species (ROS) such as superoxide radicals, hydroxyl radicals, and so on [2]. These Reactive Oxygen Species react with biomolecules and cause oxidative damage to cells. The magnitude of the damage from ionizing radiation varies greatly depending on the absorbed dose, the duration of radiation exposure, the time between exposures, and the sensitivity of the tissues to radiation [3]. Ionizing radiation damage to biomolecules occurs either through the direct effects of radiation or through the attack of short-lived reactive oxygen species resulting from radiolysis [4].

The reduction of oxygen by aerobic cells produces small amounts of various highly reactive molecules known as reactive oxygen species [5]. As a result of normal oxygen respiration, a certain amount of ROS is constantly formed in the cell. And it is necessary for the redox regulation of various functions. For example, hydrogen peroxide is of great importance in signalling and regulatory processes in the cell. Cells have an enzymatic antioxidant system against excessive free radicals. This system cleans various radiolysis products that are soluble in water and fat. In addition, this system eliminates both long-lived ROS and hydrogen peroxide. When the amount of ROS exceeds the neutralizing capacity of the antioxidant defence system, it causes oxidative stress, which damages biological molecules and leads to the need to replace them [6-8]. In addition to the production of short-lived free radicals, ionizing radiation also produces long-lived radicals in mammalian cells because it can easily oxidize proteins [9]. In the presence of oxygen, ionizing radiation damages proteins by forming oxidized protein products; some of these oxidized proteins may have half-lives of several hours or longer [9].

Çibuk et al.[10] in a study they conducted, they revealed that X-ray application in newborn rats could disrupt Caspase signalling pathways and cause infertility. The wavelength of X-rays is small and the energy is high, so it has high penetration power. Therefore, exposure to X-rays can cause the formation of free radicals. The free radicals formed can attack biological molecules in the cell, causing cellular lipid peroxidation and Deoxyribose nucleic acid (DNA) damage [11].

With the increase in free radical concentration, cells produce endogenous antioxidants (such as glutathione, catalase) to minimize damage or eliminate free radicals. With the increase in the level of exposure to ionizing radiation, the expression of antioxidant enzymes increases [12].

The liver is considered to be a highly sensitive organ to radiation, and its damage when exposed to radiation can have profound deleterious effects due to its involvement in numerous metabolic functions [13]. Studies have shown that kidney tissue is moderately radiosensitive, and damage caused by radiation exposure is eliminated by regeneration [14,15]. However, some studies have revealed that the kidneys are one of the most radiosensitive organs of the abdominal system [16]. The harmful effects of ionizing radiation on various tissues resulting from excessive ROS production are well documented [17].

Diagnostic radiology is increasingly used in the evaluation and treatment of newborns requiring intensive care. Multiple radiographic examinations are often required, depending on the baby's birth weight, gestational age, and medical problems [18].

The aim of this study was to investigate the levels of oxidative stress and antioxidants in the liver and kidney tissue of baby rats exposed to whole-body x-ray by creating a newborn rat model.

Material and Methods

Ethical Statement

This study was conducted with the permission of Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee, dated 28.12.2023 and numbered 2023/14-04.

Animals and Experimental Groups

The rats used in the study were obtained from Van Yüzüncü Yıl University Experimental Animals Unit. Fifteen Wistar Albino pregnant rats weighing 250-300 g were housed in cages with 12 h of light/dark at a temperature of 22±2°C, with food and fresh water in front of them during the trial.

In this study with a trial period of 4 weeks, rats were randomly divided into 5 groups.

Group I (control) (3 pregnant rats; the study was continued with six male and six female infant rats after birth): Pregnant rats were fed as standard, after birth, young rats were fed exclusively with breast milk for three weeks.

Group II (3 pregnant rats; the study was continued with six male and six female infant rats after birth): From the 12th day of gestation until birth, non-lethal (diagnostic 8 Grays (Gy)) dose of X-ray was applied to rats once a day [19]. After the birth, a non-lethal dose was administered to the cubs once a day for three weeks.

Group III (3 pregnant rats; the study was continued with six male and six female infant rats after birth): From the 12th day of gestation, a non-lethal (diagnostic) dose of X-ray was applied to rats every day. After birth, a non-lethal dose of X-ray was administered to the infant rats once a day for a week. After the birth, the young rats were continued to be fed with breast milk for three weeks.

Group IV (3 pregnant rats; the study was continued with six male and six female infant rats after birth): No application was applied to animals until birth, after birth, non-lethal dose of X-ray was given to the cubs every day for three weeks.

Group V (3 pregnant rats): No application was applied to the animal until birth, after birth, non-lethal dose X-ray was applied to the cubs once a day for a week.

Sample Collection and Biochemical Analysis

After the experimental application (at the end of the 4th week), 90 mg/kg ketamine HCl (Ketalar®, Pfizer, Brooklyn, New York, USA) and 10 mg/kg xylazine HCl (Rompun®, Bayer, Leverkusen, Germany) intraperitoneal was given to all rats, lying on the table in the dorso-ventral position, opening the thorax with a vertical incision in the midline, the heart was directly cannulated, and 5 mL blood samples were taken into anticoagulant and non-anticoagulant tubes. Blood samples without anticoagulant were separated by centrifugation at 4000 rpm for 5 min.

Rat livers and kidneys were homogenized in phosphate buffer (0.1 mol/L, pH=7.4). The samples were centrifuged at 10000 rpm for 20 min and the supernatant was stored at -80°C until the working day. GSH, MDA [20] concentrations and catalase activity [21] were measured spectrometrically in liver and kidney tissues on the study day.

Statistical Analysis

The "SPSS Statistic 20" package program was used in the analysis of the data. All data were given as mean (±) and standard error (SE). Analysis of variance (ANOVA) followed by Duncan's test was performed to determine if there were significant differences between the groups. Independent sample t-test was used for pairwise comparisons. It is possible to say that there is a statistically significant difference between the groups in the results where the P (sign) values are less than 0.05.

Table 1. MDA, CAT, AOPP and GSH results of liver tissue						
Parameters	**Group I (Control)**	**Group II**	**Group III**	**Group IV**	**Group V**	**P Value**
MDA (mmol/g tissue)	0.71±0.18^{b}	1.14±0.46^{a}	1.04±0.12^{a}	0.82±0.12^{ab}	1.11±0.39^{a}	0.019
CAT (U/L)	154.03±25.16^{a}	119.68±18.95^{b}	125.9±17.35^{b}	130.37±27.27^{b}	130.05±30.04^{b}	0.033
AOPP (mmol/g tissue)	82.59±8.92^{b}	96.26±7.18^{a}	96.55±10.36^{a}	95.88±8.75^{a}	95.40±10.45^{a}	0.005
GSH (µmol/g tissue)	1.44±0.33^{a}	0.92±0.3^{c}	1.1±0.19^{bc}	1.28±0.36^{ab}	1.3±0.27^{ab}	0.004

P<0.05 shows statistical significance
Different letters in the same column indicate statistical significance

Table 2. MDA, CAT, AOPP and GSH results of kidney tissue						
Parameters	**Group I (Control)**	**Group II**	**Group III**	**Group IV**	**Group V**	**P Value**
MDA (mmol/g tissue)	0.78±0.15^{bc}	1.13±0.24^{a}	0.98±0.24^{ab}	0.89±0.12^{bc}	0.76±0.25^{c}	0.002
CAT (U/L)	155.17±23.29^{a}	188.52±51.94^{a}	175.59±34.94^{a}	176.75±37.48^{a}	169.01±26.39^{a}	0.35
AOPP (mmol/g tissue)	65.45±10.79^{b}	89.4±17.22^{a}	73.29±13.43^{b}	72.7±15.05^{b}	74.29±11.29^{b}	0.007
GSH (µmol/g tissue)	1.44±0.26^{a}	1.07±0.24^{b}	1.04±0.3^{b}	1.03±0.25^{b}	1.1±0.44^{b}	0.025

P<0.05 shows statistical significance
Different letters in the same column indicate statistical significance

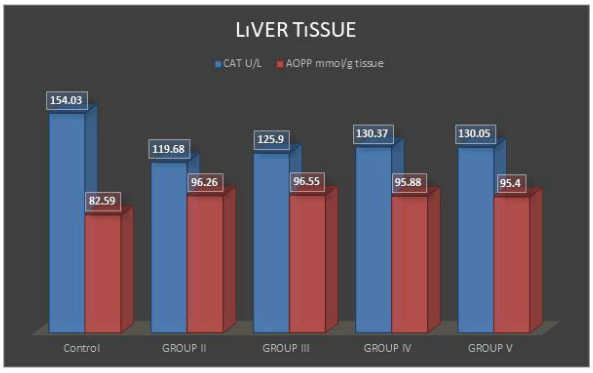

Fig 1. CAT and AOPP results of liver tissue

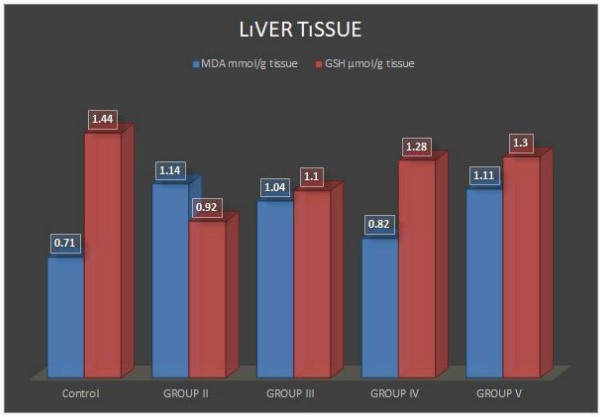

Fig 2. MDA and GSH results of liver tissue

Results

The obtained results are given in *Table1* and *Table 2*. When the results obtained from the liver tissue were examined, it was observed that the MDA level increased in all groups compared to the control group. And this increase is statistically significant (P<0.05). In addition, it was observed that the AOPP level increased significantly in the X-ray applied groups (P<0.05). Compared to the control group, a significant decrease in CAT activity and GSH amount was observed in the X-ray treated groups (P<0.05) *(Table 1, Fig. 1, Fig. 2)*.

It is observed that the amount of MDA and AOPP in the kidney tissue increased significantly in the X-ray treated groups compared to the control group. This increase is statistically significant (P<0.05). There was an increase in CAT activity in the X-ray treated groups compared to the control group, but no statistical significance was found in this increase (P>005). The amount of GSH decreased in all groups when compared with the control group. This decrease is also statistically significant (P<0.05) *(Table 2, Fig. 3, Fig. 4)*.

When liver and kidney tissue were compared, it was seen that the amount of AOPP in kidney tissue was significantly lower in control 3rd, 4th and 5th groups (P<0.05) *(Table 3)*. Although catalase levels were similar in kidney and liver tissues in the control group, it was seen that it decreased significantly in kidney tissue compared to liver tissue in experimental groups (P<0.05) *(Table 3)*. MDA levels were significantly higher in liver tissue compared to kidney

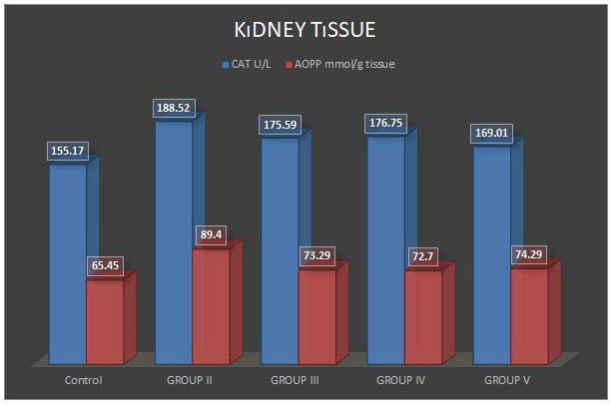

Fig 3. CAT and AOPP results of kidney tissue

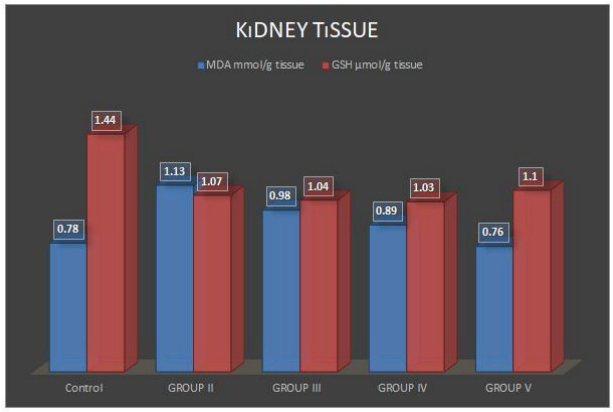

Fig 4. MDA and GSH results of kidney tissue

Table 3. *MDA, CAT, AOPP and GSH results pairwise comparison of liver and kidney tissues*

Tissues and P Value	MDAmmol/g tissue	CAT U/L	AOPP mmol/g tissue	GSH µmol/g tissue
Liver Control	0.71±0.18	154.03±25.16	82.59±8.92	1.44±0.33
Kidney Control	0.78±0.15	155.17±23.29	65.45±10.79	1.44±0.26
P Value	0.341	0.97	0.001	0.99
Liver Group II	1.14±0.46	119.68±18.95	96.26±7.18	0.92±0.3
Kidney Group II	1.13±0.24	188.52±51.94	89.4±17.22	1.07±0.24
P Value	0.97	0.002	0.27	0.24
Liver Group III	1.04±0.12	125.9±17.35	96.55±10.36	1.1±0.19
Kidney Group III	0.98±0.24	175.59±34.94	73.29±13.43	1.04±0.3
P Value	0.63	0.001	0.001	0.57
Liver Group IV	0.82±0.12	130.37±27.27	95.88±8.75	1.28±0.36
Kidney Group IV	0.89±0.12	176.75±37.48	72.7±15.05	1.03±0.25
P Value	0.21	0.005	0.001	0.096
Liver Group V	1.11±0.39	130.05±30.04	95.40±10.45	1.3±0.27
Kidney Group V	0.76±0.25	169.01±26.39	74.29±11.29	1.1±0.44
P Value	0.001	0.006	0.001	0.22

tissue in Group V ($P<0.05$) *(Table 3)*. GSH levels were significantly lower in kidney tissue compared to liver tissue in Group IV ($P<0.05$) *(Table 3)*.

Discussion

The aim of the current study was to examine oxidative stress and antioxidant levels in rats exposed to x-rays. X-ray application caused oxidative stress by increasing the levels of MDA and AOPP, which are oxidative stress parameters in the liver and kidney. At the same time, GSH levels also decreased. While liver tissue catalase activity decreased in the X-ray applied groups, it increased in kidney tissue. These findings suggest that X-ray radiation used for medical imaging may cause cellular damage in tissues in rats, increase oxidative stress, and affect the antioxidant defence system. Consistent with our study, studies in the literature reveal that repeated X-ray examinations of animals in veterinary clinics may pose potential health risks, such as acute harm and an increased cancer risk due to DNA damage [22,23].

Oxygen radicals react with polyunsaturated fatty acid (PUFA) residues in phospholipids, resulting in end products that are mostly reactive towards proteins and DNA. MDA is particularly known to play a role as a marker of oxidative stress, and its concentration is directly proportional to the cellular damage caused by free radicals [24,25]. It has been reported that low-dose X-ray may cause lipid peroxidation and cause an increase in MDA levels in rat lung and liver tissue [5]. In their study on rats, Salehi et al.[26] reported that the level of MDA increased in the serum of rats exposed to 7 Gy of x-ray for 30 days. In another study, it was shown that the level of lipid peroxidation (LPO) increased in the heart tissue of mice treated with 2 Gy X-ray for 4 days [17]. Bala et al.[27] showed that ROS

and LPO levels increased in the liver and kidney tissues of mice exposed to 2 Gy X-ray. In a study, it was revealed that ionizing radiation application affected apoptotic and oxidative stress regulatory genes in the hFOB 1.19 osteoblast cell line in a time and dose-dependent manner and that the harmful effects in this cell line might be due to mitochondrial pathway activation [28]. In a study conducted with cell culture, it was shown that gamma radiation increased ROS levels and caused apoptosis and DNA damage [29]. Ionizing radiation results in excessive ROS production due to high oxygen consumption and metabolic rate [30]. X-ray exposure results in cellular damage, either directly or indirectly, via the water radio dialysis mechanism, leading to the formation of ROS [31]. ROS affect various cellular functions by causing nucleic acid damage, oxidized proteins and lipid peroxidation [32]. In the presented study, it was found that X-ray application before and after birth (Group II) significantly increased the MDA level in liver and kidney tissue compared to the control group. Compared to the control group in Group III, liver and kidney tissue MDA levels were higher, but only liver tissue MDA levels were found to be significantly higher. In parallel with the above-mentioned studies, X-ray application increased oxidative stress and caused MDA levels to increase in liver and kidney tissue.

AOPP is a safe marker used to evaluate oxidative modification of proteins. AOPP is a marker of the severity of oxidative stress and oxidatively mediated protein damage in inflammation and is often produced during oxidative stress [33]. In the presented study, liver tissue AOPP levels in all groups treated with X-ray were found to be significantly higher than the control group. Kidney tissue AOPP level was found to be higher than the control group in the X-ray applied groups, but only Group II kidney tissue AOPP level was found to be significantly higher than the control group.

GSH is a tripeptide and non-enzymatic antioxidant produced in the body that plays a pivotal role in maintaining cellular redox balance [34]. It has been reported that GSH plays a protective role against oxidative stress by directly detoxifying H_2O_2 and lipid peroxides by scavenging hydroxyl radical and singlet oxygen, and also returns vitamins C and E, which are important antioxidants, to their active forms [35]. Decreased GSH level in tissues not only impairs cellular defence but also causes increased oxidative damage [36]. GSH deficiency is often an indicator of the presence of oxidative stress [24]. High doses of radiation lead to a decrease in GSH levels. This is thought to be due to the production of reactive oxygen and nitrogen species produced by short-lived ionizing radiation, which are then neutralized by reduced glutathione producing oxidized glutathione [24]. It was reported that the GSH content in the cardiac tissue of rats treated with 2 Gy X-ray for 4 days did not change when compared with the control group, but it decreased significantly in the lung tissue [17]. Bala et al.[27] showed that GSH levels were significantly reduced in the liver and kidney tissue of mice exposed to 2 Gy X-ray for 4 days compared to the control group. The decreased GSH activity in hepatic and renal tissues in X-ray-exposed animals may be due to its increased use in an attempt to detoxify ROS produced by ionizing radiation [27]. Decrease in GSH may cause an increase in hydroxyl radicals that attack lipid membranes [34]. In the presented study, GSH levels in the liver and kidney tissues of all groups exposed to X-ray were found to be lower than the control group. Especially liver and kidney tissue GSH levels of rats exposed to X-ray during pregnancy were found to be significantly lower compared to the control group. As the exposure time increased, the decrease in tissue GSH levels became greater. In Group IV and Group V, liver and kidney tissue GSH levels were found to be lower compared to the control group, but only kidney tissue GSH levels were found to be significant ($P<0.05$). The decrease in GSH level can be explained by the fact that X-ray exposure increases oxidative stress, which in turn decreases antioxidant capacity.

Catalase converts two molecules of hydrogen peroxide into molecular oxygen and two molecules of water. It has been shown that catalase activity in the testicular tissue of mice exposed to X-ray increased compared to the control group [34]. Another study reported that catalase activity increased in the liver and kidney tissue of mice exposed to X-ray [27]. Bala et al.[1] The increase in catalase activity in tissues may have occurred to scavenge excess ROS production due to X-ray exposure [27]. In the presented study, liver tissue catalase activity in all groups exposed to X-ray was found to be significantly lower than the control group. Especially Group II catalase activity was found to be lower than all other groups. In contrast to the liver tissue catalase activity, the X-ray exposed groups had higher catalase activity compared to the control group, but these elevations were not significant. This difference in catalase activity between tissues may depend on the tissue's response to exposure, the absorbed dose, and the sensitivity of the tissues. Additionally, the kidney is a moderately radiosensitive organ and has been reported to have the ability to regenerate after radiation-induced cytotoxic injuries [14,37]. The results obtained from this study showed that AOPP and MDA were generally higher in liver tissue *(Table 3)*. Catalase activity was higher in kidney tissue *(Table 3)*. When liver and kidney tissue were compared, it could be said that kidney tissue was more resistant to ionizing radiation than liver tissue.

In conclusion, X-ray exposure induces cellular damage in liver and kidney tissues by increasing oxidative stress and impairing the antioxidant defense system. These

findings suggest that repeated X-ray exposure in medical and veterinary settings may exacerbate cellular injury and contribute to severe health consequences, including carcinogenesis. Therefore, it is crucial to carefully evaluate the potential risks associated with X-ray exposure and minimize unnecessary imaging procedures to prevent long-term adverse effects.

Declarations

Availability of Data and Materials: The data used in this article will be provided by correspondin author (S. Ç.) upon request.

Financial Support: This study was not financially supported by any person or institution.

Ethical Statement

This study was conducted with the permission of Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee, dated 28.12.2023 and numbered 2023/14-04.

Conflict of Interest: The authors declare that they have no conflict of interest.

Declaration of Generative Artificial Intelligence (AI): The tables and figures used in this article were not created by artificial intelligence.

Author Contributions: Forming the hypothesis and planning the study: S.Ç.; Carrying out the experimental phase: A.A. & S.Ç.; Obtaining data and writing the article: A.A. & S.Ç.

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